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Continuous positive airway pressure therapy for obstructive sleep apnea reduces interictal epileptiform discharges in adults with epilepsy

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ABSTRACT

Obstructive sleep apnea (OSA) is highly prevalent, affecting 25% of men and 10% of women. We recently reported a prevalence of OSA of 30% among 130 adults with epilepsy unselected for sleep disorder complaints, including 16% with moderate-to-severe disease, rates that markedly exceed general population estimates. Treatment of OSA with continuous positive airway pressure (CPAP) therapy or upper airway surgery reduces seizures in many cases. A single study reported a reduction in interictal spike rate with CPAP in 6 patients with OSA. We explored the effect of CPAP therapy on spike rate in 9 adults with epilepsy and OSA. Interictal epileptiform discharges were quantified during a diagnostic polysomnogram (PSG) and a second PSG using therapeutic CPAP. Spike rates were calculated for each recording during wake and sleep stages. Continuous positive airway pressure therapy was associated with significant reductions in median (quartiles) spike rate overall (77.9 [59.7–90.7] %), in wakefulness (38.5 [0.3–55] %), and in sleep (77.7 [54.8–94.7] %) but not in REM sleep. Continuous positive airway pressure therapy also produced a significant improvement in oxygen saturation and arousals. Our work extends a single prior observation demonstrating beneficial effects of CPAP therapy on interictal EEG in patients with epilepsy with comorbid OSA and supports the hypothesis that sleep fragmentation due to OSA contributes to epileptogenicity.

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent condition, affecting 24% of men and 9% of women based on epidemiologic studies from nearly 2 decades ago when obesity rates were lower than the current US estimates [1]. We recently reported a prevalence of OSA (apnea–hypopnea index [AHI] on polysomnogram [PSG] of ≥10) of 30% in adults with epilepsy unselected for sleep disorder symptoms, including 16% with moderate-to-severe disease [2]. Treatment of OSA with continuous positive airway pressure (CPAP) therapy or upper airway surgery has been associated with a reduction in seizures in adults and children in uncontrolled series [3–11]. Only one prior study examined the effects of CPAP therapy on interictal EEG in patients with epilepsy [12]. Improvement in sleep continuity and reduction in spike rate during a single sleep cycle were reported in 6 subjects with OSA treated with CPAP and 2 with COPD treated with oxygen. Recurrent obstructive respiratory events in sleep increase cardiovascular and metabolic risk via a number of mechanisms including sympathetic activation, endothelial dysfunction, systemic inflammation, and metabolic dysregulation [13]. But in addition to cardiovascular consequences, OSA may increase seizure susceptibility. Proposed mechanisms include recurrent oxygen desaturation and arousals, resulting in sleep fragmentation and chronic sleep deprivation. We sought to compare the spike rate between diagnostic and therapeutic CPAP PSGs and assess the association between changes in spike rate and sleep fragmentation and oxygenation on PSG in adults with epilepsy and comorbid OSA.

2. Methods

We studied 9 adults with pharmacoresistant epilepsy (persistent seizures despite 2 or more appropriately chosen doses of antiepileptic drugs [AEDs]) and OSA (AHI ≥ 5) meeting the following criteria: 1) diagnostic PSG combined with 21-channel EEG showing interictal epileptiform discharges (IEDs), 2) PAP titration in the laboratory or autotitration in the home with identification of a CPAP setting that normalized the AHI (AHI < 5), 3) repeat PSG–EEG using therapeutic CPAP during which the pressure was altered by no more than 1 cm H_2O with all recorded pressures normalizing the AHI, and 4) no change in AED therapy or body mass index (BMI) by ≥5 kg/m^2 between diagnostic and therapeutic CPAP recordings.

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Table 1
Sample characteristics.

Subject	Age (year)	Sex	BMI (kg/m^2)	Epilepsy duration (year)	Seizure days/month (baseline)	Seizure type	Epilepsy type	Etiology	AEDs (mg)	CPAP pressure ($cm H_2O$)	Seizure days/month (CPAP)	Total spike rate (baseline)	Total spike rate (CPAP)	%Total spike rate reduction
1	27	M	32.1	12	30	CPS, GTC	Left temporal	Unknown	LTG 900, OXC 2400	8	4	257.6	103.9	59.7
2	26	M	23.8	14	30	CPS, GTC	Right temporal	FCD	GBP 2400, LTG 400, CBZ 1000	6	30	526.8	311.7	40.8
3	24	M	N/A	11	30	GTC	Gen	Genetic	ZSM 500, VPA 2000, LTG 400	11	N/A	2.9	0	100
4	44	M	30.8	16	30	CPS	Right temporal	Unknown	CBZ 1800, LTG 800	12	4	1.3	0	100
5	56	M	N/A	48	18	CPS	Left temporal	HS	LEV 2000, CBZ 1200	14	0[a]	197.7	18.3	90.7
6	19	F	36.4	18	30	CPS	Right frontal	FCD	ZSM 500, CBZ 1200	4	4[b]	345.7	84.7	75.5
7	37	M	59.5	30	16	GTC	Gen	Genetic	LTG 500, PHT 400	9	8	14	8.9	36.4
8	28	M	22.7	4	0.33	CPS, GTC	Right frontal	Unknown	LEV 3000	8	0.33	296	65.4	77.9
9	38	F	21	4	5	CPS, GTC	Right frontal	Unknown	CBZ 1400, LEV3000, LTG 400	11	4	603.1	129.8	78.5

CPAP: continuous positive airway pressure, CPS: complex partial seizure, GTC: generalized tonic–clonic seizure, Gen: generalized, FCD: focal cortical dysplasia, HS: hippocampal sclerosis, CBZ: carbamazepine, GBP: gabapentin, LTG: lamotrigine, LEV: levetiracetam, N/A: not applicable, OXC: oxcarbazepine, PHT: phenytoin, VPA: valproic acid, and ZSM: zonisamide.

[a] Temporal lobe resection performed shortly after CPAP initiation.

[b] Refused PAP after study.

Polysomnograms were recorded and scored according to standardized guidelines prior to the 2012 AASM new scoring criteria [14]. Recordings included right and left electrooculogram, single-channel electrocardiogram, submental and bilateral anterior tibialis EMG, oronasal thermistor and nasal pressure transducer, thoracic and abdominal piezoelectric belts, pulse oximetry, end-tidal CO_2, video monitoring, and snore microphone in addition to a 21-channel EEG using the 10–20 system of electrode placement. The alternate hypopnea definition ($\geq$50% reduction in amplitude of the nasal pressure signal for $\geq$10 s associated with an arousal or a $\geq$3% oxygen desaturation) was used. Obstructive sleep apnea severity was defined as mild (AHI 5–<15), moderate (AHI 15–<30), and severe (AHI $\geq$30 events per sleep hour). The median number of days from diagnostic to therapeutic CPAP PSG was 62.2 (range: 29–92).

Spike rate (IEDs per hour) was calculated for the entire recordings by dividing the number of IEDs by the time spent in each stage (wake, stage 1 [N1], stage 2 [N2], stage 3 [slow wave sleep; N3], and REM). Demographic and epilepsy-related characteristics were obtained through a review of electronic medical records. The frequency of focal and generalized seizures excluding auras was calculated as seizure days per month for the 3 months prior to the diagnostic PSG and after CPAP initiation, when available.

EEG and polysomnographic variables between diagnostic and PAP studies were compared using the Wilcoxon matched-pairs signed-rank test. Spearman's rho correlations were used to assess the linear association between spike rate and AHI, arousal index (AI) and wake time after sleep onset (WASO), both measures of sleep continuity, and mean and nadir SPO_2. Data are presented as medians and quartiles (P25–P75) for continuous variables and as percentages for categorical variables. Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. $p < 0.05$ was considered significant.

3. Results

Nine subjects (7 males) with median (P25–P75) age of 28 (26–38) years and BMI of 30.8 (22.7–36.4) kg/m^2 were included. Subjects were otherwise healthy with the exception of one with Crohn's disease and another with type II diabetes mellitus, hypertension, and hyperlipidemia. Sample characteristics are presented in Table 1. Median (P25–P75) seizure frequency (excluding auras) was 30 (16–30) days per month with epilepsy duration of 14 (11–18) years. All subjects reported snoring; 8 (89%) had excessive daytime sleepiness; and 4 (44%) had choking during sleep or witnessed apneas, prompting the diagnostic PSG.

Table 2
Baseline and CPAP polysomnographic variables.

Parameter	Baseline	CPAP	p
AHI	22.2 (17.3–33.2)	1.9 (0.7–2.4)	0.01
REM-AHI	25 (21.5–33.6)	2.6 (2.3–5.1)	0.01
Supine-AHI	22.2 (17.1–33.2)	0.9 (0–2.2)	0.01
SPO_2 nadir (%)	86 (75–89)	92 (89–92)	0.01
Mean SPO_2 (%)	94.5 (93.5–96)	95 (95–96)	0.05
Time in bed (min)	443.4 (414–490)	408.3 (379.6–469.9)	0.21
Total sleep time (min)	352.2 (310.5–422)	355.1 (322.9–365.5)	0.26
Supine time (%)	74 (46–100)	72.1 (48.3–100)	0.90
Sleep efficiency (min)	78 (72.6–82)	89 (86.3–95.8)	0.14
Sleep latency (min)	15 (5–24)	8.9 (2.5–12.3)	0.40
REM latency (min)	197 (120–236)	94.7 (80–96)	0.04
WASO (min)	85 (63–103)	22.8 (17.5–47.3)	0.09
Arousal index	24 (19–32.1)	9 (6.3–13.6)	0.01
PLM Arousal index	0 (0–0.84)	0.3 (0–18.5)	0.57
% stage 1	9.5 (6.4–17.2)	7 (2.2–8)	0.05
% stage 2	71.5 (64.5–79.2)	68 (56.5–72)	0.14
% stage 3	4.2 (1–8.6)	4.1 (1.7–11)	0.40
% REM	10.3 (7.9–13.8)	18.2 (12.3–23.2)	0.01

Data are shown as median (P25–P75). CPAP: continuous positive airway pressure; WASO: wake time after sleep onset; PLM: periodic limb movement. Wilcoxon signed-rank test.

Table 3
Spike rates on baseline and CPAP studies.

Spike rate	Baseline	CPAP	p
Total	257.6 (14–345.7)	65.4 (8.9–103.9)	0.01
Sleep	247.2 (19.7–385.5)	48.1 (8.9–116.3)	0.01
Wake	116.9 (1.1–173.9)	52 (0–81.2)	0.04
Stage 1	150.9 (8.3–320)	22.8 (0–88.7)	0.01
Stage 2	283.6 (25.6–377.8)	86.7 (1.5–118.9)	0.01
Stage 3	37 (0–217.9)	15.6 (0–79.2)	0.02
REM	37 (5.1–104.6)	28.3 (0–59.3)	0.06

Data are shown as median (P25–P75). CPAP: continuous positive airway pressure. Wilcoxon signed-rank test.

Table 2 shows respiratory and sleep parameters at baseline and after CPAP treatment. Obstructive sleep apnea was mild in 1 case and moderate or severe in 4 cases. In all cases, CPAP therapy normalized the AHI. Sleep architecture also improved with PAP therapy as exhibited by significant reductions in arousals, stage 1 sleep, and REM sleep latency and an increase in REM sleep percentage. Other features of sleep consolidation were observed, although not significant.

Table 3 and Fig. 1 show the EEG data. Spike rate was reduced with CPAP therapy by a median (P25–P75) of 77.9 (59.7–90.7) % overall, 77.7 (54.8–94.7) % in sleep, and 38.5 (0.3–55) % in wakefulness owing to significant declines in all NREM sleep stages and a trend for decline in REM sleep.

Positive correlations between the baseline AHI and total and sleep spike rates were observed ($r = 0.7$, $p = 0.04$ and $r = 0.73$, $p = 0.03$, respectively) but not between AHI and wake spike rate ($r = 0.38$, $p = 0.32$). No correlation was found between the baseline total spike rate and arousal index ($r = 0.28$, $p = 0.46$), WASO ($r = 0.07$, $p = 0.87$), mean/nadir SPO_2 ($r = 0.61$, $p = 0.11$/$r = 0.77$, $p = 0.02$), or the magnitude of spike rate reduction with CPAP therapy ($r = 0.56$, $p = 0.15$).

4. Discussion

The main findings of our study are the following: 1) therapeutic CPAP was associated with significant reductions in spike rate compared with baseline in the absence of AED changes in adults with epilepsy and OSA; 2) these reductions were observed in wakefulness and all sleep stages excluding REM sleep; 3) improvements in sleep continuity and nadir SPO_2 were also found; however, no correlation between the spike rate and these variables was observed; and 4) more severe OSA (higher AHI) was associated with higher spike rates.

Obstructive sleep apnea is characterized by recurrent upper airway obstruction in sleep resulting in arousals and oxygen desaturations. In turn, sleep fragmentation leads to a disruption in the normal sleep–wake cycle and a reduction in restorative sleep (stage 3 and REM) stages. Untreated moderate-to-severe OSA produces a state of chronic sleep deprivation leading to excessive daytime sleepiness, fatigue, and a host of cardiovascular, neurologic, and metabolic consequences [13,15]. Adults with epilepsy have a higher than expected prevalence of OSA [2,16], and treatment of OSA with CPAP is associated with a reduction in seizures in several small case series [3–11]. Although unproven, proposed mechanisms for sleep apnea-induced seizure susceptibility include recurrent oxygen desaturation and arousals, resulting in sleep fragmentation and sleep deprivation.

One prior study explored the effect of PAP on spike rate during a single sleep cycle in 6 patients with focal epilepsy and OSA immediately after application of PAP and in two with snoring and COPD treated with oxygen supplementation alone [12]. A reduction in spike rate during sleep was observed in all sleep stages but was only significant in stage 3, which has the highest spike rate of all sleep stages in patients with focal epilepsy [17–21]. Sleep fragmentation and oxygen desaturations improved with treatment. Our methodology extends these observations, increasing confidence in the demonstrated effect as 1) spike quantification was performed over an entire night of recording and 2) spike rate was quantified after subjects had been fully acclimating to CPAP and confirmed that the recommended setting normalized the AHI. In turn, we found a significant reduction in spike rate in wake and all sleep stages except for REM sleep despite the higher REM percentage with CPAP. This is not unexpected since REM sleep is a protective state for IEDs and seizures and thus, characterized by a lower spike rate than wakefulness and NREM sleep [17–23].

Continuous positive airway pressure therapy produced an improvement in sleep continuity by reducing arousals, sleep latency, WASO, and stage 1 sleep percentage and increasing REM sleep percentage in the absence of AED changes. Yet, we did not find a correlation between spike rate and oxygen saturation or sleep fragmentation parameters, possibly due to the small number of cases. Notably, our oxygen saturation analysis was limited to mean and nadir values as we were unable to collect desaturation indices. Therefore, our work does not offer insights into the precise mechanisms by which CPAP reduces epileptiform EEG abnormalities. However, a positive correlation between spike rate and AHI was observed before CPAP therapy, suggesting that OSA increases epileptogenicity in predisposed individuals. Additionally, we found no correlation between baseline spike rate and the amount of spike rate reduction after CPAP therapy, suggesting that the beneficial effects of therapy are not limited to those with frequent IEDs in sleep. Because of the retrospective nature of our study, we were unable to collect post-CPAP therapy seizure outcomes in 3 subjects (lost to follow-up, refused long-term CPAP therapy and status-post temporal lobectomy).

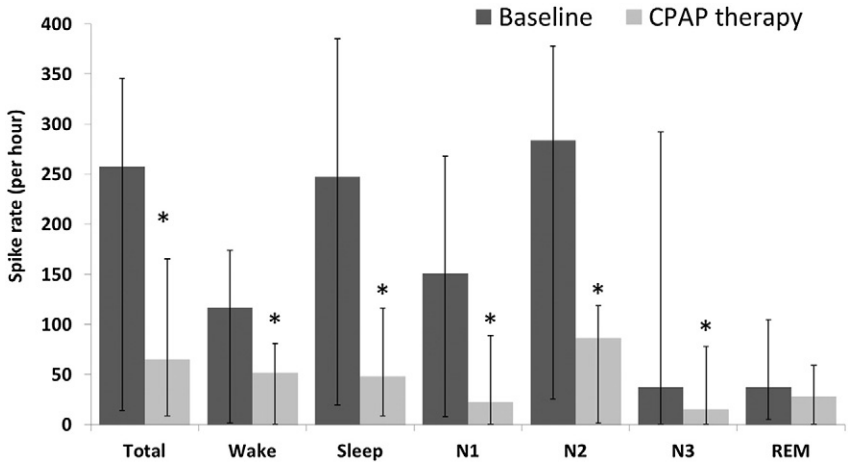

Fig. 1. Median (P25–P75) spike rates at baseline and with therapeutic CPAP therapy. *$p < 0.05$ (Wilcoxon signed-rank test).

In the 6 subjects with post CPAP seizure outcome, there was a significant reduction in seizure frequency from a median of 30 (16–30) to 4 (4–8) seizure days per month ($p = 0.05$).

The high prevalence of OSA in adults with epilepsy and growing evidence of beneficial effects of PAP therapy on seizure control support the need for early recognition and treatment of OSA in patients with epilepsy. Our work offers further evidence that OSA increases epileptogenicity that can be reversed with PAP therapy in patients with epilepsy regardless of the OSA severity and epilepsy type.

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Disclosures

We acknowledge that all coauthors have been substantively involved in the study and/or the preparation of the manuscript, no undisclosed groups or persons have had a primary role in the study and/or in manuscript preparation, and all coauthors have seen and approved the submitted version of the paper and accept responsibility for its content. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Dr. Foldvary-Schaefer receives grant support from ResMed Foundation, a PAP device company. The remaining authors have no conflicts of interest.

References

[1] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230–5.
[2] Foldvary-Schaefer N, Andrews ND, Pornsriniyom D, Moul DE, Sun Z, Bena J. Sleep apnea and epilepsy: who's at risk? Epilepsy Behav 2012;25:363–7.
[3] Beran RG, Plunkett MJ, Holland GJ. Interface of epilepsy and sleep disorders. Seizure 1999;8:97–102.
[4] Devinsky O, Ehrenberg B, Barthlen GM, Abramson HS, Luciano D. Epilepsy and sleep apnea syndrome. Neurology 1994;44:2060–4.
[5] Hollinger P, Khatami R, Gugger M, Hess CW, Bassetti CL. Epilepsy and obstructive sleep apnea. Eur Neurol 2006;55:74–9.
[6] Malow BA, Foldvary-Schaefer N, Vaughn BV, Selwa LM, Chervin RD, Weatherwax KJ, et al. Treating obstructive sleep apnea in adults with epilepsy: a randomized pilot trial. Neurology 2008;71:572–7.
[7] Malow BA, Fromes GA, Aldrich MS. Usefulness of polysomnography in epilepsy patients. Neurology 1997;48:1389–94.
[8] Malow BA, Weatherwax KJ, Chervin RD, Hoban TF, Marzec ML, Martin C, et al. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. Sleep Med 2003;4:509–15.
[9] Vaughn BV, D'Cruz OF, Beach R, Messenheimer JA. Improvement of epileptic seizure control with treatment of obstructive sleep apnoea. Seizure 1996;5:73–8.
[10] Vendrame M, Auerbach S, Loddenkemper T, Kothare S, Montouris G. Effect of continuous positive airway pressure treatment on seizure control in patients with obstructive sleep apnea and epilepsy. Epilepsia 2011;52:e168–71.
[11] Koh S, Ward SL, Lin M, Chen LS. Sleep apnea treatment improves seizure control in children with neurodevelopmental disorders. Pediatr Neurol 2000;22:36–9.
[12] Oliveira AJ, Zamagni M, Dolso P, Bassetti MA, Gigli GL. Respiratory disorders during sleep in patients with epilepsy: effect of ventilatory therapy on EEG interictal epileptiform discharges. Clin Neurophysiol 2000;111(Suppl. 2):S141–5.
[13] Drager LF, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: an emerging risk factor for atherosclerosis. Chest 2011;140:534–42.
[14] Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester: American Academy of Sleep Medicine; 2007.
[15] Caples SM, Rosen CL, Shen WK, Gami AS, Cotts W, Adams M, et al. The scoring of cardiac events during sleep. J Clin Sleep Med 2007;3:147–54.
[16] Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. Neurology 2000;55:1002–7.
[17] Bazil CW, Walczak TS. Effects of sleep and sleep stage on epileptic and nonepileptic seizures. Epilepsia 1997;38:56–62.
[18] Crespel A, Baldy-Moulinier M, Coubes P. The relationship between sleep and epilepsy in frontal and temporal lobe epilepsies: practical and physiopathologic considerations. Epilepsia 1998;39:150–7.
[19] Herman ST. Epilepsy and sleep. Curr Treat Options Neurol 2006;8:271–9.
[20] Malow BA, Lin X, Kushwaha R, Aldrich MS. Interictal spiking increases with sleep depth in temporal lobe epilepsy. Epilepsia 1998;39:1309–16.
[21] Minecan D, Natarajan A, Marzec M, Malow B. Relationship of epileptic seizures to sleep stage and sleep depth. Sleep 2002;25:899–904.
[22] Ng M, Pavlova M. Why are seizures rare in rapid eye movement sleep? Review of the frequency of seizures in different sleep stages. Epilepsy Res Treat 2013; 2013:932790.
[23] Sammaritano M, Gigli GL, Gotman J. Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. Neurology 1991;41:290–7.